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OFFICE OF WATER REGULATIONS
AND STANDARDS

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Heptachlor.

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
DWEL	Drinking water equivalent level
HA	Health advisory
LEL	Lowest-effect level
LOAEL	Lowest-observed-adverse-effect level
MCLG	Maximum contaminant level goal
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on heptachlor, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

The U.S. EPA (1987c,d) judged human carcinogenicity data to be inadequate for quantitative risk assessment. Negative or marginally positive results for cancer mortality were reported in three epidemiology studies of pesticide applicators or manufacturing workers exposed to chlordane or heptachlor or both; these studies were confounded by exposure to other chemicals or were inadequate in sample size and duration of follow-up (U.S. EPA, 1987c,d). U.S. EPA (1987c,d) cited 11 case reports from Infante et al. (1978) involving children who had pre- or postnatal exposure to heptachlor and chlordane, and who suffered blood dyscrasias, neuroblastomas and central nervous system disorders. Because of insufficient information on these cases, no conclusions could be drawn.

An additional case of cancer, a gliosarcoma in a 7-week-old boy whose mother had ingested milk containing high levels of heptachlor during gestation and while breast-feeding, was reported by Chadduck et al. (1987).

Another recent study by Epstein and Ozonoff (1987) indicates risk from exposure to heptachlor. These investigators reported 25 previously unpublished cases of blood dyscrasia among persons whose homes were treated for termites with chlordane and heptachlor. The blood dyscrasias included leukemias, production defects and thrombocytopenic purpura. Although these findings are consistent with those from 34 published cases (Epstein and Ozonoff, 1987), including those presented by Infante et al. (1978) mentioned above, the evidence of carcinogenicity for humans is still inadequate.

No case reports or epidemiologic studies of exposure specific to heptachlor epoxide were found in the available literature. Heptachlor epoxide is

not commercially available in the United States, but is a product of heptachlor oxidation (U.S. EPA, 1987d), and is found in ambient water and in certain foods (fish, milk) (U.S. EPA, 1980).

The animal data on the carcinogenicity of heptachlor are considered sufficient for risk assessment (U.S. EPA, 1987c). Long-term rat and mouse carcinogenicity studies on heptachlor have been reported. No increase in treatment-related tumors was reported in the four chronic rat studies reviewed by the CRAVE Work Group (U.S. EPA, 1987c). Positive results were obtained in two studies in mice, the more sensitive species. These studies were described in the AWQCD (U.S. EPA, 1980); however, since data from these studies were reanalyzed in a different way in the recent assessment (U.S. EPA, 1987c), those studies are reviewed briefly here. No newer, pertinent studies in animals have been located.

Davis (1965) conducted a study for the FDA on groups of 100 male and 100 female C3H mice fed heptachlor (unspecified purity) at 0 or 10 ppm levels for 2 years. (An additional group was fed heptachlor epoxide, as described in the following section of this addendum.) Survival at the end of the 2 years was only 34% among controls and 30% among experimentals. Approximately twice as many treated animals developed benign liver lesions (both hyperplasia and benign tumors) as did controls. Epstein (1976) reported a reevaluation by Reuber of the slides from the Davis (1965) study. Reuber (1987) reported a statistically significant increase in hepatocellular carcinomas in the treated males (64/87) and females (57/78), compared with the control males (22/73) and females (2/53). The findings of three other independent pathologists were similar to those of Reuber (Epstein, 1976).

Fifty male and 50 female B6C3F1 mice were exposed to technical-grade heptachlor at TWA concentrations of 6.1 and 13.8 ppm (males) and 9 and 18

ppm (females) for 80 weeks, followed by a 10-week observation period (NCI, 1977). A statistically significant increase in the incidence of hepatocellular carcinomas was found in high-dose males ($p<0.001$) and females ($p<0.005$), compared with controls.

The animal data on the carcinogenicity of heptachlor epoxide were also judged sufficient for risk assessment (U.S. EPA, 1987d). Increased incidences of hepatic carcinomas were reported in female rats in a chronic oral study in male and female CFN rats and in two oral studies in mice, the more sensitive species (U.S. EPA, 1980, 1987d). As with heptachlor, the mouse studies pertinent to quantification of the verified cancer potency factor for heptachlor epoxide were described in the AWQCD (U.S. EPA, 1980), but will be reviewed here because they are the basis for the more recent quantitative risk assessment. Newer, pertinent animal studies have not been located.

In a study for the FDA, Davis (1965) exposed two groups of 100 male and 100 female C3H mice for 2 years to dietary levels of 0 or 10 ppm heptachlor epoxide. General survival was low (50% of controls; 9.5% experimentals), with early deaths attributed to tumors. A 2-fold increase (treated animals over controls) was found in benign liver lesions (both hyperplasia and benign tumors). A reevaluation of the slides from this study by Reuber (1987) revealed highly statistically significant increases in incidences of liver carcinoma in both sexes. The incidence in males was 73/79 for the treated group and 22/73 for controls, and in females was 77/81 for the treated group and 2/53 for the controls. The carcinomas in the treated group were larger and more frequently multiple, compared with the smaller and solitary ones in controls. Reuber (1987) also diagnosed cirrhosis and hepatic vein thrombosis in the treated mice.

IRDC (1973) tested a 75:25 mixture of heptachlor epoxide:heptachlor in the diet of CD-1 mice, 100/sex/group, at dose levels of 0, 1, 5 and 10 ppm for 18 months, at which time survivors were killed. IRDC (1973) reported a significant increase of nodular hyperplasia among both sexes at the two highest doses. A reevaluation of the slides from this study by Reuber (1987) resulted in a change of diagnosis from nodular hyperplasia to carcinoma in many cases. Three independent pathologists agreed with Reuber's diagnoses (Epstein, 1976). Incidences of liver carcinomas at 0, 1, 5 and 10 ppm were 0/62, 2/61, 18/68 and 52/80 for the males and 6/76, 1/70, 6/65 and 30/57 for the females (IRDC, 1973; as reevaluated by Reuber, 1987). The tumor incidence for male CD-1 mice at 1 ppm, as shown in the dose-response data for q_1^* derivation (U.S. EPA, 1986a, 1987b,d), is listed as 2/68, but should be 2/61 (Reuber, 1987; Epstein, 1976).

The weight-of-evidence classification for the carcinogenicity of both heptachlor and heptachlor epoxide is B2 - probable human carcinogen. These classifications are verified by the Agency-wide CRAVE Work Group, and are based on induction of benign and malignant tumors in male and female mice of three strains treated with heptachlor, and on the induction of liver carcinomas in male and female mice of two strains and in female rats of one strain treated with heptachlor epoxide (U.S. EPA, 1987c,d). The U.S. EPA (1987c,d) noted that several structurally-related chemicals are also liver carcinogens.

Bioconcentration Factor (BCF)

In the 1980 AWQCD (U.S. EPA, 1980), the mean BCF value for heptachlor after normalization to 1% lipids was 3747 and the weighted average BCF (adjusted to 3% lipids) was 11,200. In 1982, the mean BCF value was changed to 5222 and the weighted average BCF was changed to 15,700 (U.S. EPA, 1982).

A measured steady-state BCF of 14,400 was obtained for heptachlor epoxide using fathead minnows (Veith et al., 1979). Similar fathead minnows contained an average of 7.6% lipids (Veith, 1980). An adjustment factor of 3.0/7.6 can be used to adjust the measured BCF from the 7.6% lipids of the fathead minnow to the 3.0% lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCF for heptachlor epoxide and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 5680. These values are currently undergoing Agency review and may be modified pending the outcome of this review.

QUANTIFICATION OF EFFECTS

Heptachlor

The ambient water quality criteria derived by U.S. EPA (1980) for heptachlor were 0.028, 0.28 and 2.78 mg/ℓ for exposure through water and fish and shellfish and 0.029, 0.29, and 2.85 ng/ℓ for exposure through fish and shellfish only. These values correspond to lifetime increased cancer risk levels of 10^{-7}, 10^{-6} and 10^{-5}, respectively. The criteria were calculated from a q_1^* of 3.37 per mg/kg/day, assuming 70 kg body weight and a daily intake of 2 ℓ of drinking water and 6.5 g fish and shellfish with a BCF for heptachlor of 11,200. The potency factor (q_1^*) was based upon dose-response data for hepatocellular carcinomas in male B6C3F1 mice (NCI, 1977). As described in the Bioconcentration Factor section, the weighted average BCF was corrected from 11,200 in the original AWQCD (U.S. EPA, 1980) to 15,700 (U.S. EPA, 1982), which resulted in a change in the criteria levels to 0.020, 0.20 and 2.04 ng/ℓ. These values apply regardless of whether exposure occurs from ingestion of water and aquatic organisms, or ingestion of aquatic organisms alone. U.S. EPA (1987a, 1988a), however, lists the original criteria rather than the corrected values.

A new slope factor (q_1^*) of 4.5 per mg/kg/day has been derived (U.S. EPA, 1986a, 1987b), verified by the Agency-wide CRAVE committee, and is available on IRIS (U.S. EPA, 1987c). This value represents the geometric mean of the following q_1^*s from four data sets showing significant increases in the incidence of hepatocellular carcinomas in mice: 12.4 and 14.9 per mg/kg/day for C3H male and female mice, respectively (Davis, 1965; reevaluated by Reuber, 1987) and 2.79 and 0.83 per mg/kg/day for B6C3F1 male and female mice, respectively (NCI, 1977).

Using the verified slope factor of 4.5 per mg/kg/day, and assuming a 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for heptachlor of 15,700 (U.S. EPA, 1982), the criteria for heptachlor in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.015	0.15	1.5	15
Consumption of fish and shellfish only	0	0.015	0.15	1.5	15

Heptachlor Epoxide

Ambient water quality criteria were not derived for heptachlor epoxide in the U.S. EPA (1980) document. Existing ambient water quality criteria for human health for heptachlor epoxide are represented in U.S. EPA (1988b) as the same as those for heptachlor, 2.8×10^{-4} µg/ℓ for water and fish consumption, and 2.9×10^{-4} µg/ℓ for fish consumption only.

Criteria may be derived specifically for heptachlor epoxide, based upon the oral slope factor of 9.1 per mg/kg/day (U.S. EPA, 1986a, 1987b), which has been verified by the CRAVE Work Group (U.S. EPA, 1987d). This slope factor (q_1^*) is the geometric mean of the following q_1^* values from four data sets showing significant increases in the incidence of hepatocellular carcinomas in mice: 27.7 and 36.2 per mg/kg/day for C3H male and female mice, respectively (Davis, 1965; reevaluated by Reuber, 1987) and 6.48 and 1.04 per mg/kg/day for CD-1 male and female mice, respectively (IRDC, 1973; reevaluated by Reuber, 1987).

Using the verified slope factor of 9.1 per mg/kg/day, and assuming a 70 kg body weight, daily consumption of 2 ℓ of water and 6.5 g fish and shellfish with a BCF for heptachlor epoxide of 5680, the criteria for heptachlor epoxide in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (ng/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.020	0.20	2.0	20
Consumption of fish and shellfish only	0	0.021	0.21	2.1	21

EXISTING STANDARDS AND CRITERIA

Heptachlor

Use of chlordane/heptachlor-containing products as pesticides was disapproved in 1987 under a Special Review, Federal Insecticide and Rodenticide Act, with a few exceptions. Uses not affected by this decision or previous suspension were: 1) subsurface application for termite control; 2) treatment of nonfood roots and tops (U.S. EPA, 1988a).

The Health Advisory Program of the Office of Drinking Water has established a 10-day HA for a child of 0.010 mg/ℓ. Insufficient data exist for establishment of a 1-day or longer-term HA for a child, but it is recommended that the 10-day HA of 0.010 be used as the 1-day HA, and that a modified DWEL (adjusted for a 10 kg child) of 0.005 mg/ℓ be used as the longer-term HA. Appropriate data are lacking for calculation of a longer-term HA for an adult as well, and it is recommended that the DWEL of 0.0175 mg/ℓ be used as such. Because heptachlor is considered to be a probable human carcinogen, no lifetime HA has been recommended (U.S. EPA, 1988a).

The proposed MCLG for heptachlor in drinking water is 0 mg/ℓ, based on carcinogenic effects (U.S. EPA, 1988a).

WHO (1984) set a drinking water guideline for heptachlor and heptachlor epoxide of 0.1 µg/ℓ.

The U.S. EPA has verified an oral RfD of 5×10^{-4} mg/kg/day for heptachlor, based upon a NOEL of 3 ppm diet (0.15 mg/kg/day) from a chronic rat study (U.S. EPA, 1987e). An RfD for inhalation exposure has not been recommended.

The verified oral slope factor for the carcinogenicity of heptachlor is 4.5 per mg/kg/day and the drinking water unit risk factor is 1.3×10^{-4}/µg/ℓ (U.S. EPA, 1987c) (see Review of New Data section).

A quantitative estimate of carcinogenic risk from inhalation exposure to heptachlor was calculated from oral carcinogenicity data and the verified oral slope factor. The verified inhalation slope factor is 4.5 per mg/kg/day, and the inhalation unit risk factor is 1.3×10^{-3}/µg/m³ (U.S. EPA, 1987c).

OSHA (1985) has published a PEL for heptachlor of 0.5 mg/m³. The ACGIH (1987) has adopted a corresponding TWA-TLV of 0.5 mg/m³. Both agencies note that the chemical can be absorbed through the skin.

The NRC (1982) has recommended an interim guideline of 2 µg/m³ for heptachlor in military housing facilities.

Heptachlor Epoxide

The Health Advisory Program of the Office of Drinking Water has determined that appropriate data for calculating 1-day and 10-day HAs for heptachlor epoxide are not available. A modified DWEL of 0.00013 mg/ℓ (adjusted for a 10 kg child) is recommended as the longer-term HA for a child; it is also recommended that the DWEL of 0.00044 mg/ℓ be used as the longer-term HA for a 70 kg adult. Because heptachlor epoxide is a carcinogen, no lifetime HA has been recommended (U.S. EPA, 1988b).

The MCLG for drinking water for this compound is 0 mg/ℓ, based on carcinogenic effects (U.S. EPA, 1988b).

WHO (1984) set a drinking water guideline for heptachlor and heptachlor epoxide at 0.1 µg/ℓ.

The U.S. EPA (1986b) has verified an oral RfD of 1.3×10^{-5} for heptachlor epoxide, based upon a LEL of 0.5 ppm in the diet (0.0125 mg/kg/day) from a study in beagle dogs. An RfD for inhalation exposure has not been recommended.

The verified oral slope factor for the carcinogenicity of heptachlor epoxide is 9.1 per mg/kg/day, and the drinking water unit risk factor is $2.6 \times 10^{-4}/\mu g/\ell$ (U.S. EPA, 1987d) (see Review of New Data section).

A quantitative estimate of carcinogenic risk from inhalation exposure was calculated from the oral data and verified oral slope factor. The inhalation slope factor is 9.1 per mg/kg/day, and the inhalation unit risk factor is $2.6 \times 10^{-3}/\mu g/m^3$ (U.S. EPA, 1987d).

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